Supplemental Table 1. Univariate hazard ratios of overall mortality within 6 months from first CMV pneumonia with 95% CI.

Variable	No failure		Failure			
	(N = 125)		(N = 296)			
	N (%)		N (%)		HR	95% CI
Patient Age (years)						
0 – 19	22	(31)	48	(69)	1.0	–
20 – 49	73	(29)	178	(71)	1.1	0.8 – 1.5
50 – 73	30	(30)	70	(70)	1.0	0.7 – 1.5
Recipient Sex						
Female	44	(23)	144	(77)	1.0	–
Male	81	(35)	152	(65)	0.7	0.6 – 0.9
Donor sex						
Female	58	(31)	127	(69)	1.0	–
Male	65	(28)	166	(72)	1.1	0.9 – 1.4
Unknown	2		3		–*	–
Ethnicity						
Non Caucasian	22	(31)	48	(69)	1.0	–

Caucasian	102	(29)	246	(71)	1.1	0.8 – 1.5
Unknown	1		2		–*	–
Year of transplantation						
1986 – 7/1992	39	(24)	122	(76)	1.0	–
8/1992 – 1999	35	(27)	93	(73)	0.9	0.7 – 1.2
2000 – 2011	51	(39)	81	(61)	0.7	0.5 – 0.9
Number of transplant procedures						
One	117	(30)	277	(70)	1.0	–
Two	6	(26)	17	(74)	1.0	0.6 – 1.6
Two in tandem	2	(50)	2	(50)	–**	–
Donor type						
HLA-matched	44	(26)	126	(74)	1.0	–
HLA-mismatched	17	(31)	38	(69)	0.9	0.6 – 1.3
Unrelated	53	(32)	115	(68)	0.8	0.6 – 1.1
Autologous	11	(39)	17	(61)	0.7	0.4 – 1.1
Conditioning regimen						
Myeloablative with combination chemotherapy	31	(31)	70	(69)	1.0	–

Myeloablative with total body irradiation	76	(28)	197	(72)	1.1	0.9 – 1.5
Nonmyeloablative	18	(38)	29	(62)	0.8	0.5 – 1.3
Stem Cell graft source						
Peripheral blood (PB) or PB + bone marrow (BM)	45	(35)	84	(65)	1.0	–
Bone Marrow or Cord blood	80	(27)	212	(73)	1.3	1.0 – 1.6
Disease risk at transplantation						
Low	55	(33)	111	(67)	1.0	–
Intermediate	11	(24)	35	(76)	1.3	0.9 – 1.9
High	57	(28)	149	(72)	1.2	0.9 – 1.5
Unknown	2		1		–*	–
Recipient CMV serostatus pretransplant						
Negative	8	(21)	31	(79)	1.0	–
Positive	117	(31)	264	(69)	0.8	0.5 – 1.1
Unknown	0		1		–*	–
Donor CMV serostatus pretransplant						
Negative	58	(30)	138	(70)	1.0	–
Positive	56	(29)	140	(71)	1.1	0.9-1.4

Unknown	0		1		–*	–
Autologous	11	(39)	17	(61)	–*	–
Forced expiratory volume before transplantation (%)						
≥ 70	94	(31)	208	(69)	1.0	–
< 70	11	(25)	33	(75)	1.1	0.8 – 1.6
Unknown	20	(27)	55	(73)	1.1	0.8 – 1.5
Lung capacity before transplantation (%)						
≥ 80	93	(31)	211	(69)	1.0	–
< 80	7	(22)	25	(78)	1.3	0.9 – 2.0
Unknown	25	(29)	60	(71)	1.0	0.7 – 1.3
Acute GvHD peak grade						
0	23	(28)	58	(72)	1.0	–
1 - 2	74	(40)	112	(60)	0.7	0.5 – 1.0
3 - 4	28	(18)	126	(82)	1.3	0.9 – 1.7
Chronic GvHD requiring systemic immunosuppression						
No	36	(15)	204	(85)	1.0	–
Yes	89	(49)	92	(51)	0.9	0.7 – 1.2

CMV pneumonia diagnosis (days after transplant)						
0 – 30	16	(23)	54	(77)	1.0	–
30 – 100	60	(29)	148	(71)	0.9	0.6 – 1.2
> 100	49	(34)	94	(66)	0.7	0.5 – 1.0
Anti-T cell therapy in 6 months prior to pneumonia						
No	118	(31)	257	(69)	1.0	–
Yes	7	(15)	39	(85)	1.7	1.2 – 2.4
Co-pathogens at time of CMV pneumonia						
None	73	(31)	161	(69)	1.0	–
Fungal or viral (+/- bacterial)	9	(22)	32	(78)	1.3	1.0 – 1.8
Bacterial only	33	(31)	72	(69)	1.0	0.7 – 1.3
Unknown	10	(24)	31	(76)	1.2	0.8 – 1.8
Treatment of CMV pneumonia						
Ganciclovir or Foscarnet	21	(29)	52	(71)	1.0	–
No treatment or CMV-Ig alone or high-dose acyclovir alone	1	(5)	21	(95)	1.9	1.2 – 3.2
CMV-Ig or IVIG + antiviral(s)	103	(32)	223	(68)	1.0	0.7 – 1.3
Mechanical ventilation at diagnosis						

No	111	(41)	160	(59)	1.0	–
Yes	11	(8)	135	(92)	3.3	2.6 – 4.1
Lymphocyte counts (cells/mm^3) in 2 weeks prior to pneumonia						
>300	42	(47)	48	(53)	1.0	–
100-300	34	(30)	81	(70)	1.6	1.1 – 2.2
Unknown	13	(38)	21	(62)	1.4	0.8 – 2.3
Bilirubin (mg/dL) within 2 weeks prior to pneumonia						
Normal range (0.1 – 1)	37	(51)	35	(49)	1.0	–
> Upper limit of normal (1)	49	(29)	119	(71)	2.0	1.4 – 2.9
> 5 × Upper limit of normal (5)	8	(10)	70	(90)	4.4	2.9 – 6.7
Unknown	31	(30)	72	(70)	2.0	1.3 – 3.0
Creatinine (mg/dL) within 2 weeks prior to pneumonia						
Normal range (0.3 – 1.2)	44	(38)	72	(62)	1.0	–
> Upper limit of normal (1.2)	48	(28)	125	(72)	1.3	0.9 – 1.7
> 2 × Upper limit of normal (2.4)	5	(12)	35	(88)	2.3	1.6 – 3.5
Unknown	28	(30)	64	(70)	1.2	0.9 – 1.7

* Patients with unknown values (or patients with autologous transplantation for donor CMV serostatus) are excluded from analysis.

** Tandem and second transplant recipients combined for analysis.

Supplemental Table 2. Multivariable analysis of overall and CMV-attributable mortality within 6 months from first CMV pneumonia, including only patients who received antivirals as treatment for CMV, with and without IVIG or CMV-specific IgG (N=395)*.

Variable	Overall mortality				CMV-attributable mortality		
	HR	95% CI	p		HR	95%CI	p
Treatment of CMV pneumonia							
Ganciclovir or foscarnet	1.0	–	–		1.0	–	–
CMV-Ig or IVIG + antiviral drug(s)	0.8	0.6-1.1	0.20		1.2	0.8-1.8	0.48
Sex							
Male	1.0	–	–		1.0	–	–
Female	1.5	1.1-1.8	0.003		1.6	1.2-2.1	0.003
Year of transplantation							
1986-7/1992	1.0	–	–		1.0	–	–
8/1992-1999	1.1	0.8-1.4	0.70		1.0	0.7-1.4	0.98
2000-2011	0.8	0.6-1.1	0.20		0.7	0.5-1.0	0.05
Acute GvHD grade							
0-2	1.0	–	–				
3,4	1.4	1.1-1.8	0.006				

Co-pathogens at time of CMV pneumonia							
None	1.0	–	–				
Fungal or viral (+/- bacteria)	1.3	1.0-1.8	0.05				
Unknown	1.0	0.6-1.6	0.85				
Mechanical ventilation at diagnosis							
No	1.0	–	–		1.0	–	–
Yes	3.3	2.6-4.3	<0.001		4.1	3.0-5.6	<0.001
Lymphocyte counts (cells/mm^3) within 2 weeks prior to pneumonia							
≥ 300	1.0	–	–		1.0	–	–
< 300	1.8	1.3-2.5	<0.001		1.7	1.1-2.6	0.02
Missing	1.4	0.8-2.6	0.24		1.7	0.9-3.2	0.11

* Both groups were statistically not different in baseline parameters with the exception of stem cell graft (peripheral blood, 55% [antiviral therapy alone] vs. 71% [combination therapy], P=0.008), lymphopenia (< 300/mm^3, 56% vs. 73%, P=0.015), donor status (unrelated or HLA mismatched donor, 63% vs. 51%, P=0.04), transplantation year (after 2000, 47% vs. 28%, P<0.001), and lymphopenia (53% vs. 72%, P=0.015). Factors that met criteria for inclusion in the multivariable model are shown in the Table.

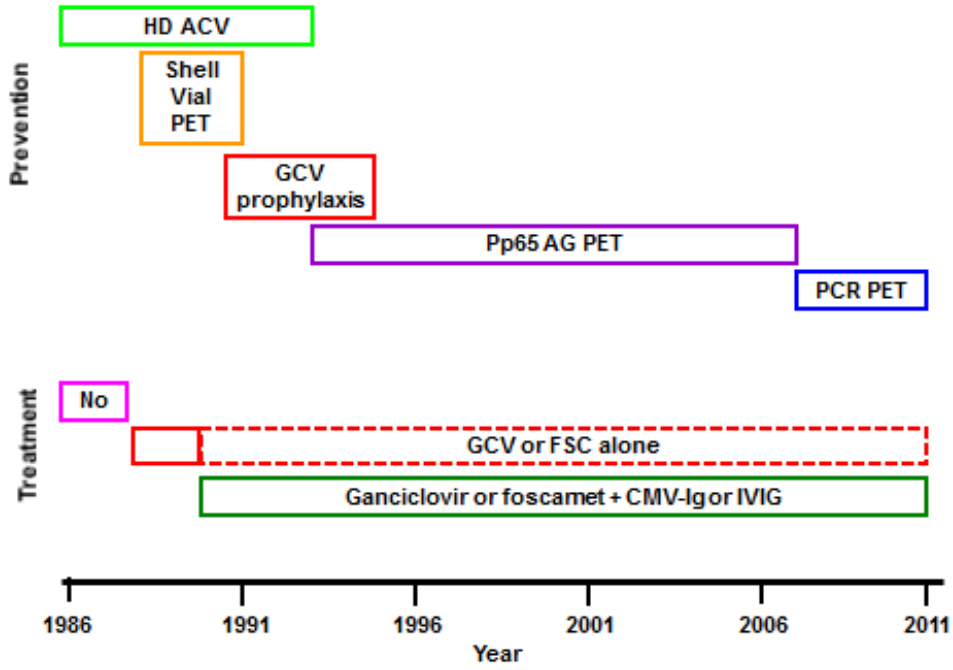
Supplemental Table 3. Multivariable analysis of overall and CMV-attributable mortality within 60 days from first CMV pneumonia, including only patients who were transplanted after July 1992, were not diagnosed by autopsy, and received antivirals as treatment for CMV, with and without IVIG or CMV-specific IgG (N=233)*.

Variable	**Overall mortality**				**CMV-attributable mortality**		
	HR	95% CI	p		HR	95%CI	p
Treatment of CMV pneumonia							
Ganciclovir or foscarnet	1.0	–	–		1.0	–	–
CMV-Ig or IVIG + antiviral drug(s)	0.9	0.6-1.3	0.45		1.1	0.6-1.8	0.81
Sex							
Male	1.0	–	–		1.0	–	–
Female	1.4	1.0-2.0	0.05		1.5	1.0-2.4	0.05
Year of transplantation							
8/1992-1999	1.0	–	–		1.0	–	–
2000-2011	0.9	0.6-1.2	0.44		0.8	0.5-1.2	0.27
Acute GvHD grade							
0-2	1.0	–	–				
3,4	1.2	0.8-1.8	0.32				
Co-pathogens at time of CMV pneumonia							

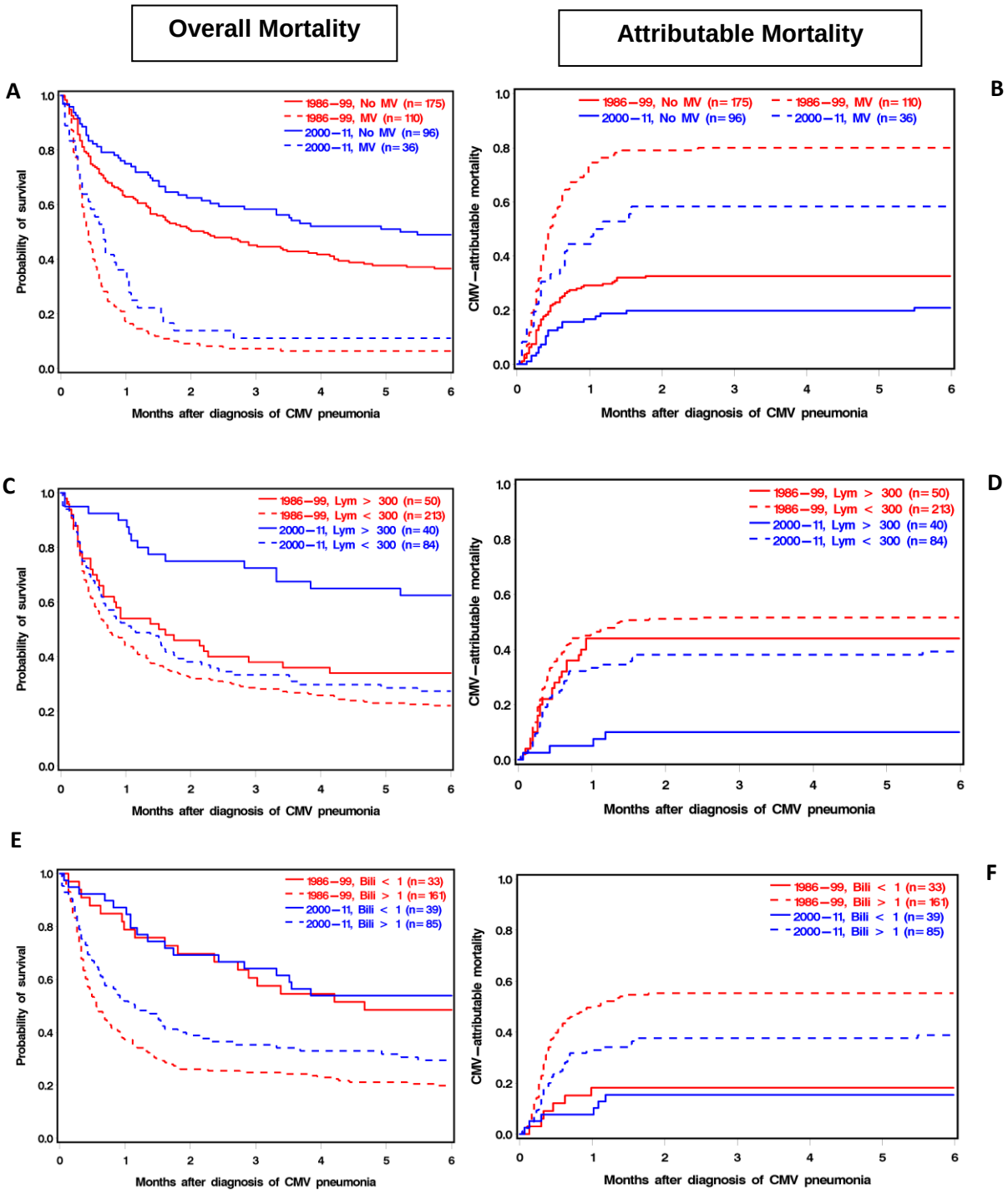
None	1.0	–	–				
Fungal or viral (+/- bacteria)	1.3	0.8-1.9	0.25				
Unknown	1.4	0.6-3.8	0.45				
Mechanical ventilation at diagnosis							
No	1.0	–	–		1.0	–	–
Yes	3.3	2.3-4.7	<0.001		3.4	2.2-5.2	<0.001
Lymphocyte counts (cells/mm^3) within 2 weeks prior to pneumonia							
≥300	1.0	–	–		1.0	–	–
<300	2.5	1.4-4.5	0.002		2.9	1.3-6.5	0.009
Missing	2.3	1.0-5.4	0.06		3.5	1.3-9.1	0.01

* Both groups were statistically not different in baseline parameters with the exception of lymphopenia (< 300/mm^3),which was less common in the antiviral therapy alone group (53% vs. 72%, P=0.013). Lymphopenia was included in the multivariable model.

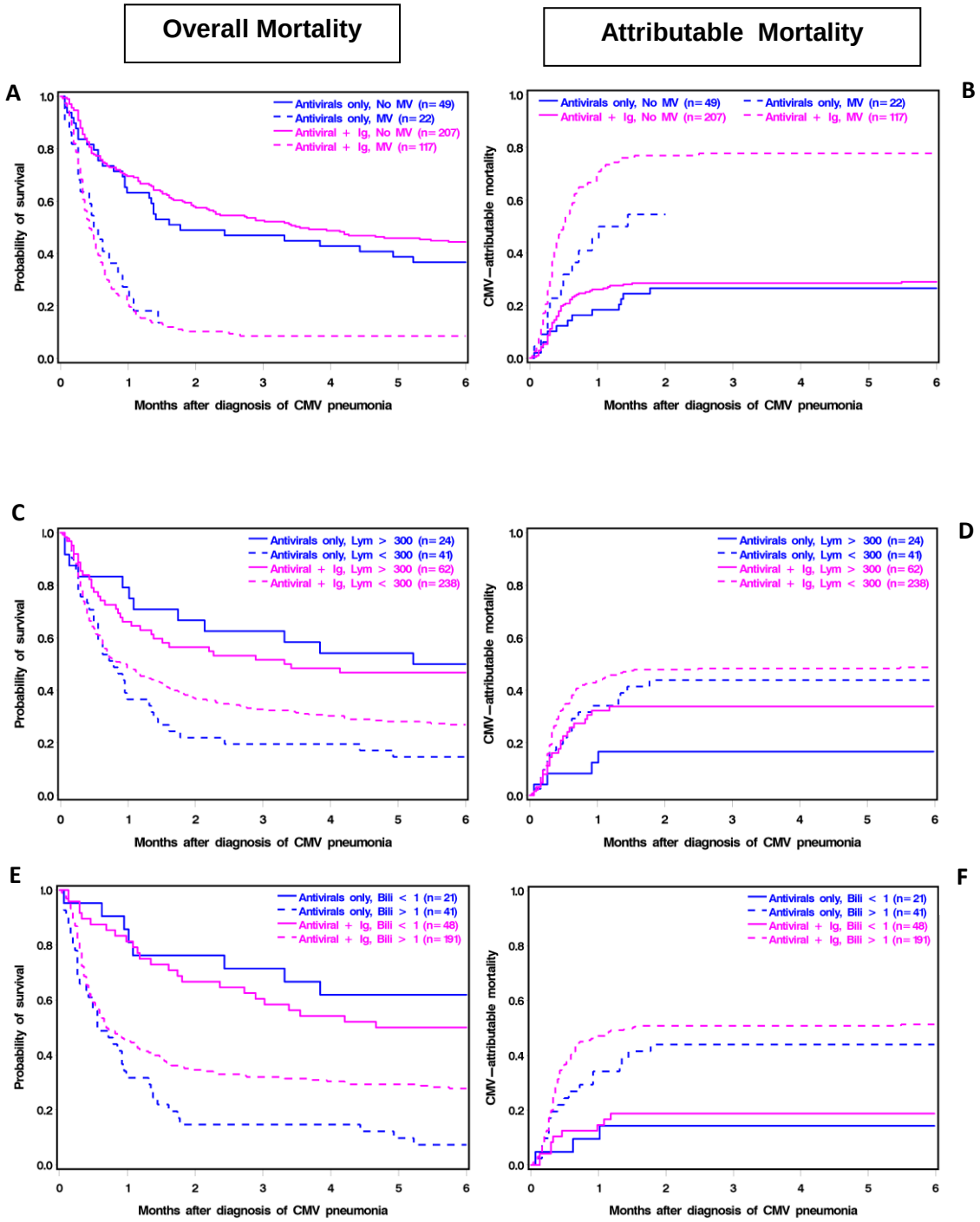
Supplemental Figure 1. Management strategies for prevention (upper panel) and treatment (lower panel) of CMV pneumonia during the study period. Overlapping strategies indicate concurrent use of strategies, usually due to randomized trials that were initially performed before the strategy was implemented. The dotted box for antiviral monotherapy indicates very occasional use of patients throughout recent years (Table 2). Abbreviations: AG, antigenemia; PCR, polymerase chain reaction; PET, preemptive therapy; GCV, ganciclovir; FSC, foscarnet, HD ACV, high-dose acyclovir (500 mg/m^2 three times daily, given intravenously).



Supplemental Figure 2. Effect of transplant period on overall (panels on the left) and CMV-attributable (panels on the right) mortality in subgroups that were significant in multivariable models: mechanical ventilation at diagnosis (A, B), lymphopenia at diagnosis (C, D), hyperbilirubinemia (E, F). Abbreviations: MV, mechanical ventilation; Lymph, absolute lymphocytes (values in cells/microliter); Bili, absolute bilirubin (values in mg/dL).



Supplemental Figure 3. Effect of adjunctive immunoglobulin treatment on overall (panels on the left) and CMV-attributable (panels on the right) mortality in subgroups that were significant in multivariable models: mechanical ventilation at diagnosis (A, B), lymphopenia at diagnosis (C, D), hyperbilirubinemia (E, F). Abbreviations: MV, mechanical ventilation; Lymph, absolute lymphocytes (values in cells/microliter); Bili, absolute bilirubin (values in mg/dL).



SUPPLEMENTATL ANALYSES

Overall Mortality

In a model restricted to patients with available data for bilirubin and creatinine (n=305), hyperbilirubinemia was independently associated with a higher risk of overall mortality after adjusting for recipient sex, grade 3-4 acute GvHD, type of antiviral treatment, mechanical ventilation, lymphocytes count, creatinine value, lung co-pathogens at CMV pneumonia onset and time period of transplantation (bilirubin >1 mg/dL *vs*. normal range, adjusted HR 1.5, 95% CI 1.0 – 2.2, p=0.07; bilirubin > 5 mg/dL *vs.* normal range, (HR 3.1, 95% CI 2.0 – 5.0, p<0.001).

In a subset of patients with available data for viral load in BAL (n=115) a viral load >2500 copies/mL compared to ≤2500 copies/mL was borderline significant association with a worse outcome (adjusted HR 1.8, 95% CI 1.0 – 3.2, p=0.06) after adjusting for CMV treatment, recipient sex, year of transplantation, grade 3-4 acute GvHD grade, mechanical ventilation at diagnosis, co-pathogen at diagnosis, and lymphocytes count.

In the subset of patients who survived at least 21 days following CMV pneumonia onset and received antiviral treatment with or without immunoglobulin products (N=344), changes in steroids dose after diagnosis was not significantly associated with overall mortality after adjusting for recipient sex, grade 3-4 acute GvHD, type of antiviral treatment, mechanical ventilation, lymphocytes count, lung co-pathogens at CMV pneumonia onset and time period of transplantation (data not shown).

In the subgroup of 49 patients with available IgG levels prior to CMV pneumonia, univariate analysis found no significant association between IgG levels at diagnosis and the risk of overall survival or CMV-attributable death (data not shown).

CMV Attributable Mortality

In a model restricted to patients with available data for bilirubin and creatinine (n=305), elevated bilirubin was independently associated with a higher risk of CMV-attributable mortality after adjusting for recipient sex, lymphopenia, type of antiviral treatment, mechanical ventilation, year of transplantation, and creatinine value, (bilirubin >1 mg/dL *vs*. normal range, HR 2.5, 95% CI 1.2 – 4.6, p=0.01; bilirubin > 5 mg/dL *vs.* normal range, HR 4.5, 95% CI 2.3 – 9.1, p<0.001).

In a subset of patients with available viral data in BAL (n=115) a viral load > 2500 copies/mL compared to ≤2500 copies/mL was not significantly associated with CMV-attributable mortality after adjusting for recipient sex, lymphopenia, CMV treatment, mechanical ventilation, and year of transplantation.

In the subset of patients who survived at least 21 days following CMV pneumonia onset and received antiviral treatment with or without immunoglobulin products (N=344), changes in steroids dose was not associated with overall mortality risk after adjusting for recipient sex, lymphopenia, use of mechanical ventilation and antiviral treatment (data not shown).